Claims 1-3 are pending in this application and have been rejected under 35 U.S.C. §112, first paragraph for "not reasonabl[y] provid[ing] enablement for all crystallizable [compositions] and crystallized complexes encompassed by the claims." Specifically, the Examiner states that the scope of the single-stranded oligonucleotide in these compositions and complexes ("a single-stranded oligonucleotide consisting of between 6 and 12 nucleotides") is not enabled.

The Examiner has rejected applicants' argument that the single-stranded oligonucleotide has limited contact with the protein (see applicants' December 3, 2001 Amendment). She points to the specification at pages 66-68 which, according ot the Examiner, refers to the fact that in the HCV NS3 helicase-d$(U)_8$ crystal "at least $dU_{4-5,7-8}$ interacts with the helicase by hydrogen bonding." Therefore, the Examiner concludes that the "identity of the single stranded oligonucleotide would seem to make a difference." Applicants traverse.

As pointed out in applicants' December 3, 2001 Amendment, the specification clearly states that:

> "Sequence specific interactions with the DNA bases are not observed within the central binding cavity of the helicase." (emphasis added; p. 71, lines 1-2).

The hydrogen bonding interaction observed by applicants is entirely consistent with this statement. Hydrogen bonding is not specific to deoxyuridine. As those of skill in the art well know, the ability of nucleotides to accept a hydrogen bond from a protein or water surrounding the nucleotide is due to the presence of oxygen atoms in the phosphate group on the nucleotide backbone – a common feature of all nucletoides [see, e.g., D. E.

Metzler, "Biocehmistry", Academic Press, New York, NY, p. 98, right column, item (3), (1977); copy enclosed]. It is that backbone phosphate hydrogen bond acceptor present in all nucleotides, not some structural feature unique to dU_8, that is responsible for the interactions between the oligonucleotide and the HCV NS3 helicase. This is set forth in the application:

> "Interaction between the ssDNA and enzyme are mostly confined to the DNA backbone, as would be expected for a nonspecific protein-nucleic acid complex.... Interestingly, these contacts arise from symmetrically equivlanet resdiues in these two domains [domains 1 and 2 of the helicase], so that protein contacts to the dU4 and dU5 backbone phosphates are nearly identical to those to the dU7 and duU8 phosphates.
>
> At the 3' end of the DNA the dU8 phosphate is stabilized by a hydrogen bond with Thr-269 Oγ.... Equivalent contacts to the dU5 phosphate are made by the Arg-393 main chain NH and Thr-411 Oγ.... The dU7 phosphate accepts a hydrogen bond from the Val-232 NH and interacts with the Ala-233 NH and Ser-231 Oγ via a bridging water molecule. The direct and water mediated main chain interactions are duplicated by Lys-371 and Lys-372 from domain 2 to the dU4 phosphate. Ser-370, the equivalent residue in domain 2 to Ser-231, makes a water mediated contact to the dU3 phosphate rather than dU4. Superposition of domains 1 and 2 of HCV helicase reveals that the residues involved in phosphate contacts are structurally equivalent (Figure 6)...." (emphasis added; p. 67, line 9 – page 68, line 12).

The interactions between the backbone phosphate residues in dU_8 and HCV helicase observed by applicants can and would be expected to occur independent of the actual nucleotide make-up of the oligonucleotide. All nucleotides have a backbone phosphate and as such all nucleotides could accept hydrogen bonds from the HCV NS3 helicase in the same manner as those in dU_8. This is further supported by the experimental evidence that poly(A), poly(G) and poly(C) all bind to the HCV NS3 helicase [Y. Gwack et al., Biochem. Biophys. Res. Comm., 225, pp. 654-69 (1996) (see particularly, p. 656, Fig 2D and p. 659, first paragraph) (copy previously submitted)].

The structural features of the HCV NS3 helicase-dU_8 interactions, and in particular the hydrogen bonding between the nucleotide backbone phosphate and certain amino acids in the helicase, as set forth in the application provide requisite assurance that any single stranded oligonucleotide of between 6 and 12 baseswould be capable of forming a crystallized complex with an HCV NS3 helicase protein. This is so irrespective of the individual nucleotides that make up such an oligonucleotide. Accordingly, claims 1-3 are fully enabled by the specification as filed and meet the requirements of 35 U.S.C. §112, first paragraph.

Applicants respsectfully request that the Examiner consider the foregoing remarks and allow pending claims 1-3 to pass to issue.

Respectfully submitted,

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